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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/903,248	Wands et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *29-36 and 39-58* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *29-36 and 39-58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jul 7, 2001* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *8*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-28, 37 and 38 have been canceled. Claim 34 has been amended. Claims 39-58 have been added. Claims 29-36, and 39-58 are pending and examined on the merits.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

3. The disclosure is objected to because of the following informalities:

(A) The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. The specification contains numerous recitations of HAAH. One species of HAAH is identified in Table 1 as SEQ ID NO:2, encoded by SEQ ID NO:3 (Table 2). The specification refers to other species of HAAH encoded by cDNAs in Table 4 (page 47). When the specification of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Without a sequence identifier, it is unclear if a reference to HAAH in the specification is synonymous with SEQ ID NO:2. Appropriate correction is required.

(B) Page 6, line 16 contains a blank space after "SEQ ID NO".

Appropriate correction is required.

Claim Objections

4. Claims 29, 30, 33, 39, 45, 49, 53 and 57 are objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. Claims 29, 30, 33, 39, 45, 49, 53 and 57 recite HAAH. Table 1 identified HAAH as SEQ ID NO:2. When the claims of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Appropriate correction is required.

5. Claims 52 and 57 are objected to because of the following informalities:

Claim 52 spells diphtheria incorrectly as "diptheria".

Claim 57 is missing a verb. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 29, 30, 33-36, 42, 43, 48, 49, 51, 52, 56, 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are rended vague and indefinite by recitation of "HAAH" as the only means of identifying the protein to which the claimed antibodies bind. The use of laboratory designations only to identify a particular protein renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct proteins. Amendment of the claims to incorporate a sequence identifier would overcome this rejection.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 31, 32, 39, 40, 41, 44-47, 50, 53, 54, 55 and 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to provide an enabling disclosure without complete evidence either that the claimed biological materials are know and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the hybridoma cell line producing the monoclonal antibodies designated 5C7, 5E9, 19B, 48A, 74A, 78A, 86A, HA238A, HA221, HA239, HA241, HA329, HA355 and FB50. It is not clear that monoclonal antibodies possessing the identical properties of 5C7, 5E9, 19B, 48A, 74A, 78A, 86A, HA238A, HA221, HA239, HA241, HA329, HA355 are known and are publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, page 1) states "The in vivo antibody response is heterogeneous and is made up of a large mixture of antibodies secreted from a polyclonal population of cells. In addition, because the differentiation of B cells involves the random rearrangements of gene segments and somatic mutation of these rearranged genes,....no two animals, even of an inbred strain will make an identical set of antibodies." Although the applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive antibodies and hybridomas identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtained the claimed antibodies and hybridomas.

Although FB50 is known in the art through publication by a member of the instant inventive entity, the M.P.E.P. (2403) states:

> The mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 CFR 1.808(b)), that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. Ex parte Hildebrand, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990).

Thus, in order to satisfy the requirements of 35 U.S.C. 112, first paragraph, a deposit of FB50 is required.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the

deposited hybridomas are producing the monoclonal antibodies 5C7, 5E9, 19B, 48A, 74A, 78A, 86A, HA238A, HA221, HA239, HA241, HA329, HA355 and FB50 as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited hybridomas are producing the identical monoclonal antibodies 5C7, 5E9, 19B, 48A, 74A, 78A, 86A, HA238A, HA221, HA239, HA241, HA329, HA355 and FB50 as described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

10. Claims 29, 30, 33-36, 42, 43, 48, 49, 51, 52, 56 and 57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification provides a written description of the protein of SEQ ID NO:2 encoded by the cDNA of SEQ ID NO:3. The protein is identified as a human Aspartyl(Asparaginyl) beta Hydroxylase. The specification sets forth SEQ ID NO:2 as HAAH but does not always refer to HAAH as SEQ ID NO:2. When given the broadest reasonable interpretation, the claims drawn to HAAH embody allelic and splice variants as well as fragments of HAAH formed from post-translational cleavage. For example, is known in the art that HAAH undergoes post translational cleavage to produce a smaller protein (Radosevitch, U.S. 6,166,176, column 3, lines 1-10) but there is no written description of the fragment produced thereby. Further, the claims do not limit HAAH by function or enzymatic activity. Claim 30 is drawn to an epitope within a catalytic site. The specification disclose only one catalytic site for HAAH in Table 1, said catalytic site responsible for the hydroxylation activity of SEQ ID NO:2. No other catalytic site are described by the specification or any art of record. Thus the claims are based on a genus of HAAH which is highly variant and catalytic sites beyond the hydroxylation site which are undisclosed. The specification provides a written description of SEQ ID NO:2 and the catalytic site at residues 678-697 responsible for hydroxylation activity, and this is inadequate to

support claims to a genus of HAAH molecules or any alternative catalytic site. The nature of protein variants produced by allelic sequences, splice variants or post-translational processing is that they are variant structure where the structure and function of one example does not provide guidance to the structure and function of the other members of the genus and the specification provides no teachings to describe any other members of the genus. According to these facts one of skill in the art would conclude that the applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is therefore insufficient to support the claims.

11. Claims 33, 45-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a monoclonal antibody that binds to an epitope of SEQ ID NO:2 linked to a cytotoxic agent, wherein the cytotoxic agent is a chemotherapeutic agent which preferentially kills tumor cells compared to non-tumor cells, does not reasonably provide enablement for a monoclonal antibody that binds to an epitope of SEQ ID NO:2 linked to a cytotoxic agent, wherein the cytotoxic agent is an agent which does kill tumor cells in preference to non-tumor cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 33, 48 and 49 are drawn to a monoclonal antibody which binds to an epitope of HAAH linked to a cytotoxic agent, wherein said composition preferentially kills tumor cells compared to non-tumor cells. Claims 45-47 and 50 specifically embody FB50 and fragments thereof as the monoclonal antibody. Claims 51 and 52 embody the monoclonal antibody of claim 33 wherein the cytotoxic agent is ricin and diphtheria toxin, respectively. The art teaches (see the rejection under 35 U.S.C. 102 (b) below) that Labyrinthin contains an extracellular portion which binds the antibody MCA 44-3A (Radosevich, (US 6,166,176, column 4, lines 49-45). The art also teaches that said extracellular portion is identical to resides 59-313 of the instant HAAH as described by SEQ ID NO:2, with the exception of a substitution of Asp for Glu at residue 312 (see Sequence 2 of Patent No 6166176 and Figure 3). It can be seen from Figure 2 of

Radosevitch that the common sequence has two membrane anchoring domains the HAAH. Radosevitch et al teaches that the Labyrinthin protein is not internalized by the cancer cell when bound by an antibody ('176, column 4, lines 46-49).

Raso et al (US 5,830,478) teach that toxic proteins from plants and bacteria such as diptheria toxin (column 2, lines 9-16) are efficient cytotoxic agents for cell killing, because they can bind to the cell membrane, and penetrate into the cytosol. However, these agents do not discriminate between cells types because the receptors to which they bind are common to many cell types (column 1, lines 13-19). Thus, it is reasonable to conclude that toxic agents such as ricin or diphtheria toxin would not discriminate between tumor and non-tumor cells. Raso et al teach that it is necessary to target these toxins into specific tissues in order to avoid non-specific interactions with non-targeted tissues (column 1, lines 36-40). Thorpe et al (US 5,660,827) teach that in circumstances where the target antigen is not internalized by the cell upon binding of an antibody, it is advantageous to target chemotherapeutic agents such as anti-tumor agents in place of toxin compounds (column 44, lines 40-46). Thorpe et al teach that the targeted chemotherapeutic agents offer added selectivity to the anti-tumor agent by means of the targeting agent (column 44, lines 46-53). Sinkule et al (Tumour Biology, 1991, Vol. 12, pp. 198-206, page 203 under the heading "Discussion") teach that doxorubicin conjugated to the monoclonal antibody 44-3A6 results in an immunoconjugate with anti-tumor activity in vitro, although the antigen recognized by said antibody in not internalized (especially page 204, first column, first full paragraph, lines 9-13). The abstract of Tomida et al teaches that most anticancer drugs are effective against rapidly dividing cells (lines 11-14). Thus it is reasonable to conclude that the efficacy of the anthracyclin, doxorubicin, is augmented by targeted delivery of doxorubicin to the periphery of the tumor where its cytotoxic effect against rapidly dividing tumor cells can be concentrated. Further, it is reasonable to conclude that it is not necessary for the antibody-doxorubicin conjugate to be internalized by the antigen on the cell surface in order for this selective anti-tumor effect to be attained as it is taught by Sinkule that the MCA 44-3A6-doxorubicin conjugate was cytotoxic in vitro against adenocarcinoma cell lines (Table 2) although the antibody was not internalized. Further, the teachings of Thorpe et al direct one of skill in the

art to substitute chemotherapeutic agents in place of plant of bacterial toxins in immunoconjugates which bind to an antigen which is not internalized.

It can be concluded from comparison of SEQ ID NO:2 and figure 2 of Radosevich with HAAH that both Labyrinthin and HAAH contain two identical membrane anchoring domains. Labyrinthin is clearly not internalized by antibody binding and it would be reasonable to conclude that the instant HAAH containing the same extracellular portion from residues 59 to 255 and the identical membrane anchoring domains would also not be internalized by binding with an antibody. The specification does not teach a working example to provide evidence to the contrary, or to provide evidence that ricin or diphtheria toxin immunoconjugates would exert a preferential cytotoxicity against tumor cells expressing HAAH. Given the above teachings of the prior art and given the lack of a working example or any evidence to the contrary, one of skill in the art would nor know how to use the claimed composition wherein the cytotoxic moiety was indiscriminate between tumor cells and non-tumor cells, such as plant or bacterial toxins, for the preferential killing of tumor cells versus non-tumor cells.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 29 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Radosevich et al (Cancer Research, 1985, Vol. 45, pp. 5808-5812) as evidenced by Radosevitch (U.S. 6,166,176, reference A1 of the I.D.S. filed November 21, 2001). Claim 29 is drawn to a monoclonal antibody which binds to an epitope of HAAH. Claim 43 is drawn to the antibody of

claim 29, wherein the epitope is on the cell surface. Radosevitch et al (1985) discloses the monoclonal antibody 44-3A6 which reacts with a cell surface antigen on a human lung carcinoma cell line, A549. Radosevitch ('176) discloses that this antibody binds to an epitope from residues 117-123 of Labyrinthin, which has an identical domain with HAAH (figure 3). Residues 117-123 in Labyrinthin are residues 175-181 of HAAH. Monoclonal antibody 44-3A6 would therefore bind to a cell surface epitope of the instant HAAH.

14. Claims 29, 33, 43 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Sinkule et al (Tumour Biology, 1991, Vol. 12, pp. 198-206) as evidenced by Radosevitch (U.S. 6,166,176, reference A1 of the I.D.S. filed November 21, 2001) and the abstract of Tomida et al (Anti-Cancer Drug Design, 1999, Vol. 14, pp. 169-172). The embodiments of claims 29 and 43 are recited above. Claim 33 is drawn to a composition comprising a monoclonal antibody that binds to an epitope of HAAH linked to a cytotoxic agent, wherein said composition preferentially kills tumor cells compared to non-tumor cells. Claim 49 is drawn to the composition of claim 33 wherein the antibody binds to an HAAH epitope on the surface of a cell.

Sinkule et al disclose the immunoconjugate consisting of monoclonal antibody 44-3A6 conjugated to doxorubicin which exhibits specific toxicity in vitro against a tumor cell line expressing the A549 antigen to which said antibody binds (Table 2, especially lines 3 and 5). Sinkule et al do not specifically disclose that the immunoconjugate would preferentially kill tumor cell in preference to non-tumor cells. However, it is know in the art, as evidenced by the abstract of Tomida et al (lines 11-14), that anti-tumor agents such as doxorubicin are effective against rapidly dividing cells, therefore it is reasonable to conclude that the immunoconjugate would preferentially kill tumor cells compared to non-tumor cells.

Radosevitch et al (1985) discloses the monoclonal antibody 44-3A6 which reacts with a cell surface antigen on a human lung carcinoma cell line, A549. Radosevitch ('176) discloses that this antibody binds to an epitope from residues 117-123 of Labyrinthin, which has an identical domain with HAAH (figure 3). Residues 117-123 in Labyrinthin are residues 175-181 of HAAH.

Thus the immunoconjugates disclosed by Sinkule et al would bind to an external epitope of HAAH.

15. Claims 29, 43 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, reference C19 of the I.D.S. submitted November 21, 2001). Claim 29 is drawn to a monoclonal antibody which binds to an epitope of HAAH. Claim 43 embodies the antibody of claim 29 wherein said epitope is on the cell surface. Claim 44 embodies the antibody of claim 29, wherein said antibody is FB50.

Lavaissiere et al disclose the monoclonal antibody FB-50 which binds to HAAH (page 1316, second column, under the heading "Molecular cloning of the antigen: its identification as HAAH". Lavaissiere et al disclose that the epitope recognized by FB-50 is on the cell surface (page 1320, first column, lines 1-5).

16. Claims 29 and 42 are rejected under 35 U.S.C. 102(a) as being anticipated by Carter et al (WO 99/01020).

Claim 29 is drawn to a monoclonal antibody which binds to an epitope of HAAH. The specification describes HAAH as SEQ ID NO:2 (Table 1, pages 5-6). Claim 42 is drawn to the antibody of claim 29 wherein the antibody is a single chain Fv molecule. Carter et al disclose monoclonal antibodies and single chain antibodies which bind to the proteins encoded by Gene 14 (page 25, line s 19-21, page 46, lines 23-31, page 83, line 5 to page 84, line 22 and page 102, lines 35-36). Carter et al disclose that the translation product of Gene 14 shares sequence homology with aspartyl beta-hydroxylase (page 24, lines 13-14). Carter et al disclose that the proteins encoded by Gene 14 include SEQ ID NO:90, SEQ ID NO:93 and SEQ ID NO:48 (page 24, lines 19-21, 23-24 and page 25, lines 5-6). Carter et al disclose a preferred epitope as SEQ ID NO:48. Residues 44-70, 85-109, and 53-70 of the instant SEQ ID NO:2 are identical to residues 1-27 of SEQ ID NO:48, residues 21-45 of SEQ ID NO:90 and residues 1-18 of SEQ ID NO:93. It is reasonable to conclude that the monoclonal antibodies or fragments thereof disclosed by Carter et al would also bind to SEQ ID NO:2 as protein sequences comprising 27, 25 and 18

amino acids are contained in the proteins encoded by Gene 14 and the instant SEQ ID NO:2. Further, Carter et al discloses SEQ ID NO:48 as comprising a preferred epitope and Carter et al defines an "epitope" a polypeptide fragment having antigenic or immunogenic activity in an animal, especially in a human and further defines an "antigenic epitope" as the region of a protein to which an antibody can bind (page 45, line 34 to page 46, line 1). Carter et al states that antigenic epitopes contain a sequence of at least 7, preferably nine and more preferable between about 15 to about 30 amino acids. The common polypeptide sequences comprise 27, 25 and 18 amino acids, falling within the range defined "more preferably" as an antigenic epitope. It is reasonable to conclude that monoclonal antibodies raised against SEQ ID NO:90, 48 and 93 of Carter et al would include monoclonal antibodies which bind to SEQ ID NO:2 as common antigenic epitopes are present within SEQ ID NO:2.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 29, 34-36, 42, 43, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radosevich et al (Cancer Research, 1985, Vol. 45, pp. 5808-5812) as evidenced by Radosevitch (U.S. 6,166,176) in view of Wels et al (U.S. 5,939,531) and Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134).

Claim 29 is drawn to a monoclonal antibody which binds to an epitope of HAAH. Claim 42 is drawn to the antibody of claim 29, wherein said antibody is a single chain Fv molecule. Claim 43 is drawn to the antibody of claim 29 wherein said epitope is on the cell surface. Claim 34 is drawn to a kit for the diagnosis of a tumor in a mammal, comprising a monoclonal antibody that binds to an epitope of HAAH. Claim 56 is drawn to the kit of claim 34 wherein said antibody is a single chain molecule. Claim 57 is drawn to the kit of claim 34 wherein said HAAH epitope on the surface of a cell. Claim 35 is drawn to the kit of claim 34 wherein said antibody is immobilized on a solid phase. Claim 36 is drawn to the kit of claim 35 wherein said solid phase is selected from the group consisting of an assay plate, an assay well, a nitrocellulose membrane, a bead, a dipstick and a component of an elution column.

Wels et al teach kits comprising recombinant antibodies for the qualitative and quantitative determination of the c-erbB-2 protein for the diagnosis and treatment of tumors (column 22, lines 1-16 and abstract). Wels et al teach that the kits further comprise buffers, detergents, pipettes, reaction vessels, calibration curves, instruction manuals and the like. Wels et al teach that an enzyme immunoassay would be carried out by coating a suitable carrier such as the plastic surface of a microtiter plate or a test tube, nitrocellulose sheets, glass or plastic beads with the monoclonal antibody of the invention, thus fulfilling the specific embodiments of claims 35 and 36 drawn to enzyme immobilization on a assay plate, assay well, a nitrocellulose membrane, and a bead (column 21, lines 10-19). Wels et al teach that the antibodies are specific for the extracellular domain of the c-erbB-2 protein (column 3, lines 53-54). Wels et al teach that the antibodies of the invention comprise single-chained antibodies (column 3, lines 12-18). Wels et al do not teach antibodies which bind to an extracellular epitope of HAAH.

Radosevich et al (Cancer Research, 1985, Vol. 45, pp. 5808-5812) as evidenced by Radosevitch (U.S. 6,166,176) anticipates claims 29 and 43 for the reasons set forth in section 13 above. Radosevitch et al teach that the binding of the 44-3A6 monoclonal antibody was a marker for adenocarcinoma (column 3, line 50 to column 4, line 19). Neither Radosevitch (1985) nor Radosevitch ('176) specifically teach a single chain antibody which will bind to HAAH, or a kit comprising said antibody.

Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134, especially page 122, first column, first full paragraph, lines 15-26) teaches advantages of single-chained antibodies over parent monoclonal antibodies which include rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially in reference to the avoidance of renal toxicity associated with drug conjugated antibodies, increased penetration of tumor masses, reduced immunogenicity due to lack of antibody effector domains (page 122, second column, lines 2-23) and relative ease of production (lines 27-30).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the monoclonal antibody 44-3A6 for the monoclonal antibodies disclosed by Wels et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Radosevitch on the presence of the antigen for 44-3A6 on adenocarcinoma cells and the teachings of Schlom on the advantages of a single chained antibody relative to the parent murine antibody in the detection and treatment of tumors, in addition to the relative ease of making said single chain antibody.

19. Claims 29, 33, 42, 43, 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sinkule et al (Tumour Biology, 1991, Vol. 12, pp. 198-206) as evidenced by Radosevitch (U.S. 6,166,176, reference A1 of the I.D.S. filed November 21, 2001) and the abstract of Tomida et al (Anti-Cancer Drug Design, 1999, Vol. 14, pp. 169-172) in view of Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular

Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134). The combination of Sinkule et al and Radosevich and Tomida anticipates the embodiments of claims 29, 33, 43 and 49 for the reason set forth in section 14 above.

Claim 42 is drawn to the antibody of claim 29, wherein said antibody is a single chain Fv molecule. Claim 48 is drawn to the composition of claim 33, wherein said antibody is a single chain Fv molecule.

Sinkule et al teach that immunoconjugates of clinically useful drugs, such as doxorubicin, chemically linked to tumor selective antibodies may ultimately be useful to treat cancer (page 199, first column, first paragraph). Neither Sinkule et al nor Radosevich et al nor Tomida teach single chain Fv antibodies of 44-3A6.

Schlom teaches the advantages of single chain antibodies over the parent murine antibodies comprise rapid clearance from the blood and body to avoid unwanted by-stander tissue toxicity, reduced accumulation in the kidneys, especially for the avoidance of renal toxicity associated with drug conjugated antibodies, increased penetration of tumor masses, reduced immunogenicity due to lack of antibody effector domains (page 122, second column, lines 2-23) as well as relative ease of production (lines 27-30).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to exchange the 44-3A6 antibody for a single chain Fv molecule conjugated to doxorubicin. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Schlom et al on the improvements associated with the administration in vivo of a single chain antibody versus the parent murine antibody, especially in reference to the lack of accumulation of single chained antibodies in the kidneys to avoid the avoidance of renal toxicity associated with drug conjugated antibodies, as well as the relative ease of producing said single chain antibodies.

20. Claims 29, 30, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, reference C19 of the I.D.S. submitted November 21, 2001) in view of Goding (Monoclonal Antibodies,

Principles and Practice, 1986, pp. 1-4) and Radosevich (U.S. 6,166,176, reference A1 of the I.D.S. filed November 21, 2001). The embodiment of claims 29, 43 and 44 are set forth above. Claim 30 is drawn to the antibody of claim 29 wherein said epitope is within the catalytic site of HAAH.

Lavaissiere et al teach the specific embodiments of claims 29, 43 and 44 for the reasons set forth in section 15, above. Lavaissiere et al teach a monospecific antiserum directed against the carboxyl terminal catalytic domain of bovine HAAH, wherein said antiserum binds to human cells (page 1320, last line to page 1321, line 5 and Legend for figure 7). Lavaissiere et al teach that this monospecific antiserum binds to the carboxyl terminus of HAAH, containing the catalytic domain for hydroxylation, in contrast to the monoclonal antibody FB-50 which binds to the amino terminus. Lavaissiere et al teach that measurements of the enzymatic hyroxylation in carcinoma cells is substantially higher than in normal cells and that immunoblots of tumor tissues also revealed an increase in hydroxylase protein in the malignant tissue (page 1321, first column, first and second full paragraphs). Lavaissiere et al do not teach a monoclonal antibody that binds to a catalytic site of HAAH.

Radosevitch (U.S. 6,166,176) teaches that Labyrinthin shares a common extracellular domain with HAAH, but is lacking the 3' region containing the enzymatic site (figure 2). Radosevitch teaches that HAAH is responsible for the modification of specific aspartic acids within the epidermal growth factor domains of proteins (column 3, lines 11-18).

Goding teaches the improvements afforded by the substitution of monoclonal antibodies in place of polyclonal antibodies. Goding teaches that monoclonal antibodies are superior to polyclonal antibodies because it is possible to reliably produce unlimited quantities of a specific antibody having the necessary fine specificity, degree of cross-reaction, affinity and physical properties in contrast to polyclonal antisera which was difficult, unreliable and required highly purified antigen (page 1, line 25 and page 3, lines 1-9).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a monoclonal antibody which would bind to the catalytic domain of HAAH. One of ordinary skill in the art would have been motivated to do so with a

reasonable expectation of success by the teachings of Goding on the improvements afforded by the substitution of monoclonal antibodies for polyclonal antiserum and the teachings of Lavaissiere et al on the correlation between elevated levels of hydroxylase activity and carcinoma cell lines and malignant tissue and the teachings of Radosevitch (U.S. 6,166,176) on the amino terminus of HAAH having the catalytic hydroxylation domain which is lacking in Labyrinthin. One of skill in the art would have been motivated to make a specific antibody which would bind to the carboxyl terminus of HAAH to avoid cross-reactivity to Labyrinthin, and attain an accurate measurement of the amount of HAAH protein in a sample, as levels of Labyrinthin would not be correlated with hydroxylation.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentable distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over,

the reference claim(s). See, e.g. *In re Berg*, 140 F. 3d 1428, 46 USPQ2d 1226 (Fed Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

23. Claims 29, 31, 39, 43, 44 and 34, 57 and 58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 35 and 39-43 of co-pending Application No. 09/859,604 in view of Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, reference C19 of the I.D.S. submitted November 21, 2001).

In the instant application claims 29, 31, 39, 43 and 44 are anticipated by claim 35 of the '604 application drawn in part to the antibodies of 86A, 5C7, 19B, FB50 and a fragment of FB50. Claim 43 is drawn to the antibody of claim 29 wherein said epitope is on the surface of the cell. Lavaissiere et al disclose that the epitope recognized by FB50 is on the cell surface (page 1320, first column, lines 1-5). Thus it is inherent in claim 35 of the '604 application that the FB50 antibody binds to an epitope on the surface of a cell.

Further, it is obvious that the instant claims 34, 57 and 58, drawn to a kit comprising a monoclonal antibody that binds to an epitope of HAAH, an kit comprising an antibody which binds to an epitope of HAAH on the cell surface and kits comprising the FB50 antibody are obvious species of the kits comprising antibodies of claim 39-43 of the '604 application. It would have been obvious to one of skill in the art to use the FB50 monoclonal antibody in a kit to bind to HAAH because Lavaissiere et al teach that the FB50 monoclonal antibody binds to a cell surface epitope of HAAH.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 29, 31, 34-36, 39-44 and 53-58 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 35 and 39-43 of U.S. Patent No.09/859,604 in view of Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, reference C19 of the I.D.S. submitted November 21, 2001) and Schlom (Monoclonal

Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1991, Ed. S. Broder, pp. 95-134) and Wels (US 5,939,531). Claims 29, 31, 39, 43 and 44 are anticipated by claims 35 of the '604 application and claims 34, 57 and 58 are obvious over claims 39-43 of the '604 application for the reasons set forth above. Claim 40 is drawn to the FB50 fragments of Fab or (Fab)2. Claim 41 is drawn to a FB50 single chain Fv molecule. Claim 42 is drawn to a single chain antibody which binds HAAH. Claim 35 and 36 specifically embody immobilization of the antibodies of the kit of claim 34, wherein the solid phase is selected from the group consisting of an assay plate, an assay well, a nitrocellulose membrane, a bead, a dipstick and a component of an elution column. Claim 53 is drawn to a kit comprising a FB50 fragment. Claim 54 is drawn to a kit comprising a Fab or (Fab')2 fragment of FB50. Claim 55 is drawn to kit comprising a single chain FB50 molecule. Claim 56 is drawn to a kit comprising a single chain Fv molecule that binds to an epitope of HAAH.

The antibodies of claim 35 of the '604 application fail to incorporate the specific embodiments of Fab, (fab')2 and sc Fv fragments of FB50, or a single chain Fv molecule that binds to HAAH.

The kits comprising antibodies of claims 39-43 of the '604 application fail to incorporate the specific embodiments of a monoclonal antibody, single chain Fv molecules, and fragments of FB50 consisting of Fab, (Fab)2 and FB50 single chain Fv molecules, as well as the embodiments of claim 35 and 36 drawn to the immobilization of the antibody on a solid phase

Lavaissiere et al teach that the FB50 monoclonal antibody binds to a cell surface epitope of HAAH.

Schlom teaches the improvements afforded by the substitution of antibody fragments such as Fab, (Fab)2 or single chain Fv for whole IgG molecules in diagnostic tumor targeting (page 97, second column, last paragraph).

Wels et al teach that an enzyme immunoassay would be carried out by coating a suitable carrier such as the plastic surface of a microtiter plate or a test tube, nitrocellulose sheets, glass or plastic beads with the monoclonal antibody of the invention (column 21, lines 10-19).

It is obvious that claims 40-42 are species of claim 35 of the '604 application drawn to FB50 fragments. It is obvious that claims 34-36 and 53-56 are species of claims 39-43 of the '604 application. One of skill in the art would be motivated to make Fab, (Fab')2 and scFv fragments of FB50 due to the teachings of Lavaissiere et al on the FB50 monoclonal antibody and the teachings of Schlom on the general improvements afforded to diagnostic assays by substituting Fab, (Fab')2 and scFv fragments in place of whole IgG antibodies. One of skill in the art would have been further motivated to include a assay plate, assay well, a nitrocellulose membrane, and a bead to the claimed kits as Wels et al teach that these are suitable carriers for monoclonal antibodies used in immunoassays.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. All claims are rejected.

Conclusion

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

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